FDA-2252 (Transmittal of Periodic Reports for Drugs for Human Use) which may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857, and is required to include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval which ends on the anniversary date. The report is required to contain the following:

(i) *Summary.* A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of the new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study.

(ii) *Distribution data.* Information about the quantity of the drug product distributed under the approved application, including that distributed to distributors. The information is required to include the National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and the quantities distributed for domestic use and the quantities distributed for foreign use. Disclosure of financial or pricing data is not required.

(iii) *Labeling.* Currently used professional labeling, patient brochures or package inserts (if any), a representative sample of the package labels, and a summary of any changes in labeling that have been made since the last report listed by date in the order in which they were implemented, or if no changes, a statement of that fact.

(iv) *Chemistry, manufacturing, and controls changes.* (*a*) Reports of experiences, investigations, studies, or tests involving chemical or physical properties, or any other properties of the drug (such as the drug's behavior or properties in relation to microorganisms, including both the effects of the drug on microorganisms and the effects of microorganisms on the drug). These reports are only required for new information that may affect FDA's previous conclusions about the safety or effectiveness of the drug product.

(*b*) A full description of the manufacturing and controls changes not requiring a supplemental application under § 314.70 (b) and (c), listed by date in the order in which they were implemented.

(v) *Nonclinical laboratory studies.* Copies of unpublished reports and summaries of published reports of new toxicological findings in animal studies and in vitro studies (e.g., mutagenicity) conducted by, or otherwise obtained by, the applicant concerning the ingredients in the drug product. The applicant shall submit a copy of a published report if requested by FDA.

(vi) *Clinical data.* (*a*) Published clinical trials of the drug (or abstracts of them), including clinical trials on safety and effectiveness; clinical trials on new uses; biopharmaceutic, pharmacokinetic, and clinical pharmacology studies; and reports of clinical experience pertinent to safety (for example, epidemiologic studies or analyses of experience in a monitored series of patients) conducted by or otherwise obtained by the applicant. Review articles, papers describing the use of the drug product in medical practice, papers and abstracts in which the drug is used as a research tool, promotional articles, press clippings, and papers that do not contain tabulations or summaries of original data should not be reported.

(*b*) Summaries of completed unpublished clinical trials, or prepublication manuscripts if available, conducted by, or otherwise obtained by, the applicant. Supporting information should not be reported. (A study is considered completed 1 year after it is concluded.)

(vii) *Status reports.* A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

(3) *Other reporting* -- (i) *Advertisements and promotional labeling.* . The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product's current professional labeling. Form FDA-2253 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

(ii) *Special reports.* Upon written request the agency may require that the applicant submit the reports under this section at different times than those stated.

(c) *General requirements* -- (1) *Multiple applications.* For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2) *Patient identification.* Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

(d) *Withdrawal of approval.* If an applicant fails to make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

§ 314.90 Waivers.

(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under § § 314.50 through 314.81. An applicant may ask FDA to waive under § 314.126(c) any criteria of an adequate and well-controlled study described in § 314.126(b). A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The waiver request is required to contain one of the following:

(1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;

(2) A description of an alternative submission that satisfies the purpose of the requirement; or

(3) Other information justifying a waiver.

(b) FDA may grant a waiver if it finds one of the following:

(1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;

(2) The applicant's alternative submission satisfies the requirement; or

(3) The applicant's submission otherwise justifies a waiver.

Subpart C -- FDA Action on Applications

§ 314.100 Time frames for reviewing applications.

(a) Within 180 days of receipt of an application, the Food and Drug Administration will review it and send the applicant either an approval letter under § 314.105, an approvable letter under § 314.110, or a not approvable letter under § 314.120. This 180-day period is called the "review clock."

(b) During the review period an applicant may withdraw an application under § 314.65 and later resubmit it. FDA will then follow the same procedure as if a new application were submitted.

(c) The time period may be extended by mutual agreement between FDA and an applicant or, as provided in § 314.60, as the result of a major amendment.

§ 314.101 Filing an application.

(a) Within 60 days after the Food and Drug Administration receives an application, the agency will determine whether the application may be filed. The filing of an application means that FDA has made a threshold determination that the application is sufficiently complete to permit a substantive review.

(b) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for refusing to file the application apply, the agency will file the application and notify the applicant in writing. The date of filing will be the date 60 days after the date FDA received the application. The date of filing begins the 180-day period described in section 505(c) of the act. This 180-day period is called the "filing clock."

(c) If FDA refuses to file the application, the agency will notify the applicant in writing and state the reason under paragraph (d) or (e) of this section for the refusal. If FDA refuses to file the application under paragraph (d) of this section, the applicant may request in writing within 30 days of the date of the agency's notification an informal conference with the agency about whether the agency should file the application. If following the informal conference the applicant requests that FDA file the application (with or without amendments to correct the deficiencies), the agency will file the application over protest under paragraph (b) of this section, notify the applicant in writing, and review it as filed. If the application is filed over protest, the date of filing will be the date 60 days after the date the applicant requested the informal conference. The applicant need not resubmit a copy of an application that is filed over protest. If FDA refuses to file the application under paragraph (e) of this section, the applicant may amend the application and resubmit it and the agency will make a determination under this section whether it may be filed.

(d) FDA may refuse to file an application if any of the following applies.

(1) The application does not contain a completed application form.

(2) The application is not submitted in the form required under § 314.50 or § 314.55.

(3) The application is incomplete because it does not on its face contain information required under section 505(b)(1), (2), (3), (4), (5), and (6) or section 507 of the act and § 314.50 or § 314.55.

(4) The application does not contain an environmental impact analysis report analyzing under § 25.1 the environmental impact of the manufacturing process and the ultimate use or consumption of the drug.

(5) The application does not contain an accurate and complete English translation of each part of the application that is not in English.

(6) The application does not contain a statement for each nonclinical laboratory study that it was conducted in compliance with the requirements set forth in Part 58, or, for each study not conducted in compliance with Part 58, a brief statement of the reason for the noncompliance.

(7) The application does not contain a statement for each clinical study that it was conducted in compliance with the institutional review board regulations in Part 56, or was not subject to those regulations, and that it was conducted in compliance with the informed consent regulations in Part 50; or, if the study was subject to but was not conducted in compliance with those regulations, the application does not contain a brief statement of the reason for the noncompliance.

(e) The agency will refuse to file an application if any of the following applies:

(1) The drug product that is the subject of the submission is already coverd by an approved application.

(2) The submission purports to be an abbreviated application under § 314.55, but the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under § 314.55(b). FDA will file a copy of the application as a citizen petition under § 10.30 seeking a finding under § 314.55 that an abbreviated application is acceptable for the drug product, and so notify the applicant in writing.

(3) The drug product is subject to licensing by FDA under the Public Health Service Act (58 Stat. 632 as amended *(42 U.S.C. 201* et seq.)) and Subchapter F of Chapter I of Title 21 of the Code of Federal Regulations.

(f) (1) Within 180 days after the date of filing, plus the period of time the review period was extended (if any), FDA will either (i) approve the application or (ii) issue a notice of opportunity for hearing if the applicant asked FDA to provide it an opportunity for a hearing on an application in response to an approvable letter or a not approvable letter.

(2) This paragraph does not apply to applications that have been withdrawn from FDA review by the applicant.

§ 314.102 Communication between FDA and applicants.

(a) *General principles.* During the course of reviewing an application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. Communications shall be appropriately documented in the application in accordance with § 10.65. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

(b) *Notification of easily correctable deficiencies.* FDA reviewers shall make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The agency will also inform applicants promptly of its need for more data or information or for technical changes in the application needed to facilitate the agency's review. This early communication is intended to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. Such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency managers as well as reviewing staff. Instead, these major scientific issues will ordinarily be addressed in an action letter.

(c) *Ninety-day conference.* Approximately 90 days after the agency receives the application, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to inform applicants of the general progress and status of their applications, and to advise applicants of deficiencies which have been identified by that time and which have not already been communicated. This meeting will be available on applications for all new chemical entities and major new indications of marketed drugs. Such meetings will be held at the applicant's option, and may be held by telephone if mutually agreed upon.

(d) *End-of-review conference.* At the conclusion of FDA's review of an application, as designated by the issuance of an approvable or not approvable letter, FDA will provide applicants with an opportunity to meet with agency reviewing officials. The purpose of the meeting will be to discuss what further steps need to be taken by the applicant before the application can be approved. This meeting will be available on all applications, with priority given to applications for new chemical entities and major new indications for marketed drugs. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application.

(e) *Other meetings.* Other meetings between FDA and applicants may be held, with advance notice, to discuss scientific, medical, and other issues that arise during the review process. Requests for meetings shall be directed to the director of the division responsible for reviewing the application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times. However, "drop-in" visits (i.e., an unannounced and unscheduled visit by a company representative) are discouraged except for urgent matters, such as to discuss an important new safety issue.

§ 314.103 Dispute resolution.

(a) *General.* The Food and Drug Administration is committed to resolving differences between applicants and FDA reviewing divisions with respect to technical requirements for applications as quickly and amicably as possible through the cooperative exchange of information and views.

(b) *Administrative and procedural issues.* When administrative or procedural disputes arise, the applicant should first attempt to resolve the matter with the division responsible for reviewing the application, beginning with the consumer safety officer assigned to the application. If resolution is not achieved, the applicant may raise the matter with the person designated as ombudsman, whose function shall be to investigate what has happened and to facilitate a timely and equitable resolution. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are contained in a staff manual guide that is publicly available under FDA's public information regulations in Part 20.

(c) *Scientific and medical disputes.* (1) Because major scientific issues are ordinarily communicated to applicants in an approvable or not approvable letter pursuant to § 314.110 or § 314.120, respectively, the "end-of-review conference" described in § 314.102(d) will provide a timely forum for discussing and resolving, if possible, scientific and medical issues on which the applicant disagrees with the agency. In addition, the "ninety-day conference" described in § 314.102(c) will provide a timely forum for discussing and resolving, if possible, issues identified by that date.

(2) When scientific or medical disputes arise at other times during the review process, applicants should discuss the matter directly with the responsible reviewing officials. If necessary, applicants may request a meeting with the appropriate reviewing officials and management representatives in order to seek a resolution. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. Requests for such meetings shall be directed to the director of the division responsible for reviewing the application. FDA will make every attempt to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

(3) In requesting a meeting designed to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other consultants, as designated by the agency. Applicants may also bring their own consultants. For major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of is standing advisory committees for its consideration and recommendations.

§ 314.104 Drugs with potential for abuse.

The Food and Drug Administration will inform the Drug Enforcement Administration under section 201(f) of the Controlled Substances Act *(21 U.S.C. 801)* when an application is submitted for a drug that appears to have an abuse potential.

§ 314.105 Approval of an application.

(a) The Food and Drug Administration will approve an application and send the applicant an approval letter if none of the reasons in § 314.125 for refusing to approve the application apply. The date of the agency's approval letter is the date of approval of the application. When FDA sends an applicant an approval letter for an antibiotic, it will promulgate a regulation under § 314.300 providing for certification of the drug, if necessary. A new drug product or antibiotic may not be marketed until an approval letter is issued. Marketing of an antibiotic need not await the promulgation of a regulation under § 314.300.

(b) FDA will approve an application and issue the applicant an approval letter (rather than an approvable letter under § 314.110) on the basis of draft labeling if the only deficiencies in the application concern editorial or similar minor deficiencies in the draft labeling. Such approval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.

(c) FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for those drugs demand flexibility in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet them. FDA makes its views on drug products and classes of drugs available through guidelines, recommendations, and other statements of policy.

§ 314.106 Foreign data.

(a) *General.* The acceptance of foreign data in an application generally is governed by § 312.20.

(b) *As sole basis for marketing approval.* An application based solely on foreign clinical data meeting U.S. criteria for marketing approval may be approved if: (1) The foreign data are applicable to the U.S. population and U.S. medical practice; (2) the studies have been performed by clinical investigators of recognized competence; and (3) the data may be considered valid without the need for an on-site inspection by FDA or, if FDA considers such an inspection to be necessary, FDA is able to validate the data through an on-site inspection or other appropriate means. Failure of an application to meet any of these criteria will result in the application not being approvable based on the foreign data alone. FDA will apply this policy in a flexible manner according to the nature of the drug and the data being considered.

(c) *Consultation between FDA and applicants.* Applicants are encouraged to meet with agency officials in a "presubmission" meeting when approval based solely on foreign data will be sought.

§ 314.110 Approvable letter to the applicant.

In selected circumstances it is useful at the end of the review period for the Food and Drug Administration to indicate to the applicant that the application is basically approvable providing certain issues are resolved. An approvable letter may be issued in such circumstances. FDA will send the applicant an approvable letter if the application substantially meets the requirements of this part and the agency believes that it can approve the application if specific additional information or material is submitted or specific conditions (for example, certain changes in labeling) are agreed to by the applicant. The approvable letter will describe the information or material FDA requires or the conditions the applicant is asked to meet. As a practical matter, the approvable letter will serve in most instances as a mechanism for resolving outstanding issues on drugs that are about to be approved and marketed. Within 10 days after the date of the approvable letter, the applicant shall either:

(a) Amend the application or notify FDA of an intent to file an amendment. The filing of an amendment or notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period for 45 days after the date FDA receives the amendment. The extension is to permit the agency to review the amendment.

(b) Withdraw the application. FDA will consider the applicant's failure to respond within 10 days to an approvable letter to be a request by the applicant to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

(c) For a new drug, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFN-360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application under § 314.105 or refuse to approve the application under § 314.125 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act.

(d) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act.

(e) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a), (b), (c), or (d) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

§ 314.120 Not approvable letter to the applicant.

The Food and Drug Administration will send the applicant a not approvable letter if the agency believes that the application may not be approved for one of the reasons given in § 314.125. The not approvable letter will describe the deficiencies in the application. Within 10 days after the date of the not approvable letter, the applicant shall either:

(a) Amend the application or notify FDA of an intent to file an amendment. The filing of an amendment or a notice of intent to file an amendment constitutes an agreement by the applicant to extend the review period under § 314.60.

(b) Withdraw the application. FDA will consider the applicant's failure to respond within 10 days to a not approvable letter to be a request by the applicant to withdraw the application under § 314.65. A decision to withdraw the application is without prejudice to refiling.

(c) For a new drug, ask the agency to provide the applicant an opportunity for a hearing on the question of whether there are grounds for denying approval of the application under section 505(d) of the act. The applicant shall submit the request to the Division of Regulatory Affairs (HFN-360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Within 60 days of the date of the not approvable letter, or within a different time period to which FDA and the applicant agree, the agency will either approve the application under § 314.105 or refuse to approve the application under § 314.125 and give the applicant written notice of an opportunity for a hearing under § 314.200 and section 505(c)(2) of the act on the question of whether there are grounds for denying approval of the application under section 505(d) of the act.

(d) For an antibiotic, file a petition or notify FDA of an intent to file a petition proposing the issuance, amendment, or repeal of a regulation under § 314.300 and section 507(f) of the act.

(e) Notify FDA that the applicant agrees to an extension of the review period under section 505(c) of the act, so that the applicant can determine whether to respond further under paragraph (a), (b), (c), or (d) of this section. The applicant's notice is required to state the length of the extension. FDA will honor any reasonable request for such an extension. FDA will consider the applicant's failure to respond further within the extended review period to be a request to withdraw the application under § 314.65. A decision to withdraw an application is without prejudice to a refiling.

§ 314.125 Refusal to approve an application.

(a) The Food and Drug Administration will refuse to approve the application and for a new drug give the applicant written notice of an opportunity for a hearing under § 314.200 on the question of whether there are grounds for denying

approval of the application under section 505(d) of the act, or for an antibiotic publish a proposed regulation based on an acceptable petition under § 314.300, if:

(1) FDA sends the applicant an approvable or a not approvable letter under § 314.110 or § 314.120;

(2) The applicant requests an opportunity for hearing for a new drug on the question of whether the application is approvable or files a petition for an antibiotic proposing the issuance, amendment, or repeal of a regulation; and

(3) FDA finds that any of the reasons given in paragraph (b) of this section apply.

(b) FDA may refuse to approve an application for any of the following reasons:

(1) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

(2) The investigations required under section 505(b) or 507 of the act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(3) The results of the tests show that the drug is unsafe for use under the conditions prescribed, recommended, or suggested in its proposed labeling or the results do not show that the drug product is safe for use under those conditions.

(4) There is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.

(5) There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling.

(6) The proposed labeling is false or misleading in any particular.

(7) The application contains an untrue statement of a material fact.

(8) The drug product's proposed labeling does not comply with the requirements for labels and labeling in Part 201.

(9) The application does not contain bioavailability or bioequivalence data required under Part 320.

(10) A reason given in a letter refusing to file the application under § 314.101(d), if the deficiency is not corrected.

(11) The drug will be manufactured or processed in whole or in part in an establishment that is not registered and not exempt from registration under section 510 of the act and Part 207.

(12) The applicant does not permit a properly authorized officer or employee of the Department of Health and Human Services an adequate opportunity to inspect the facilities, controls, and any records relevant to the application.

(13) The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in Parts 210 and 211.

(14) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(15) A nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations in Part 58 and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(16) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in Part 56 or informed consent regulations in Part 50, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

§ 314.126 Adequate and well-controlled studies.

(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of sections 505 and 507 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs and antibiotics. Therefore, the study report should provide sufficient details of study design, conduct, and analysis to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

(b) An adequate and well-controlled study has the following characteristics:

(1) There is a clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results. In addition, the protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used. If the protocol does not contain a description of the proposed methods of analysis, the study report should describe how the methods used were selected.

(2) The study uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect. The protocol for the study and report of results should describe the study design precisely; for example, duration of treatment periods, whether treatments are parallel, sequential, or crossover, and whether the sample size is predetermined or based upon some interim analysis. Generally, the following types of control are recognized:

(i) *Placebo concurrent control.* The test drug is compared with an inactive preparation designed to resemble the test drug as far as possible. A placebo-controlled study may include additional treatment groups, such as an active treatment control or a dose-comparison control, and usually includes randomization and blinding of patients or investigators, or both.

(ii) *Dose-comparison concurrent control.* At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control. Dose-comparison trials usually include randomization and blinding of patients or investigators, or both.

(iii) *No treatment concurrent control.* Where objective measurements of effectiveness are available and placebo effect is negligible, the test drug is compared with no treatment. No treatment concurrent control trials usually include randomization.

(iv) *Active treatment concurrent control.* The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient. An active treatment study may include additional treatment groups, however, such as a placebo control or a dose-comparison control. Active treatment trials usually include randomization and blinding of patients or investigators, or both. If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug.

(v) *Historical control.* The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

(3) The method of selection of subjects provides adequate assurance that they have the disease or condition being studied, or evidence of susceptibility and exposure to the condition against which prophylaxis is directed.

(4) The method of assigning patients to treatment and control groups minimizes bias and is intended to assure comparability of the groups with respect to pertinent variables such as age, sex, severity of disease, duration of disease, and use of drugs or therapy other than the test drug. The protocol for the study and the report of its results should describe

how subjects were assigned to groups. Ordinarily, in a concurrently controlled study, assignment is by randomization, with or without stratification.

(5) Adequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data. The protocol and report of the study should describe the procedures used to accomplish this, such as blinding.

(6) The methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response.

(7) There is an analysis of the results of the study adequate to assess the effects of the drug. The report of the study should describe the results and the analytic methods used to evaluate them, including any appropriate statistical methods. The analysis should assess, among other things, the comparability of test and control groups with respect to pertinent variables, and the effects of any interim data analyses performed.

(c) The Director of the Center for Drugs and Biologics may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(d) For an investigation to be considered adequate for approval of a new drug, it is required that the test drug be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(e) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

§ 314.150 Withdrawal of approval of an application.

(a) The Food and Drug Administration will notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act under the procedure in § 314.300, if any of the following applies:

(1) The Secretary of Health and Human Services has suspended the approval of the application for a new drug on a finding that there is an imminent hazard to the public health. FDA will promptly afford the applicant an expedited hearing following summary suspension on a finding of imminent hazard to health.

(2) FDA finds:

(i) That clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application was approved; or

(ii) That new evidence of clinical experience, not contained in the application or not available to FDA until after the application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or

(iii) Upon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application was approved, that there is a lack of substantial evidence from adequate and well-

controlled investigations as defined in § 314.126, that the drug will have the effect it is purported or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; or

(iv) That the application contains any untrue statement of a material fact.

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application under section 505(e) of the act and under the procedure in § 314.200, or, for an antibiotic, rescind a certification or release, or amend or repeal a regulation providing for certification under section 507 of the act and the procedure in § 314.300, if the agency finds:

(1) That the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain required records or to make required reports under section 505(j) or 507(g) of the act and § § 314.80 and 314.81, or that the applicant has refused to permit access to, or copying or verification of, its records.

(2) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the agency.

(3) That on the basis of new information before FDA, evaluated together with the evidence available when the application was approved, the labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular; and the labeling was not corrected by the applicant within a reasonable time after receipt of written notice from the agency.

(4) That the applicant has failed to comply with the notice requirements of section 510(j)(2) of the act.

(5) That the applicant has failed to submit bioavailability or bioequivalence data required under Part 320.

(6) The application does not contain an explanation of the omission of a report of any investigation of the drug product sponsored by the applicant, or an explanation of the omission of other information about the drug pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

(7) That any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its labeling was not conducted in compliance with the good laboratory practice regulations in Part 58 and no reason for the noncompliance was provided or, if it was, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

(8) Any clinical investigation involving human subjects described in the application, subject to the institutional review board regulations in Part 56 or informed consent regulations in Part 50, was not conducted in compliance with those regulations such that the rights or safety of human subjects were not adequately protected.

(c) FDA will withdraw approval of an application if the applicant requests its withdrawal because the drug subject to the application is no longer being marketed, provided none of the conditions listed in paragraphs (a) and (b) of this section apply to the drug. FDA will consider a written request for withdrawal under this paragraph to be a waiver of an opportunity for hearing otherwise provided for in this section. Withdrawal of approval of an application under this paragraph is without prejudice to refiling.

(d) FDA may notify an applicant that it believes a potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing otherwise provided for under this section, to permit FDA to withdraw approval of the application for the product, and to remove voluntarily the product from the market. If the applicant agrees, the agency will not make a finding under paragraph (b) of this section, but will withdraw approval of the application in a notice published in the Federal Register that contains a brief summary of the agency's and the applicant's views of the reasons for withdrawal.

§ 314.152 Notice of withdrawal of approval of an application for a new drug.

If the Food and Drug Administration withdraws approval of an application for a new drug, FDA will publish a notice in the Federal Register announcing the withdrawal of approval.

§ 314.160 Approval of an application for which approval was previously refused, suspended, or withdrawn.

Upon the Food and Drug Administration's own initiative or upon request of an applicant, FDA may, on the basis of new data, approve an application which it had previously refused, suspended, or withdrawn approval. FDA will publish a notice in the Federal Register announcing the approval.

§ 314.170 Adulteration and misbranding of an approved drug.

All drugs, including those the Food and Drug Administration approves, or provides for certification of, under sections 505, 506, and 507 of the act and this part, are subject to the adulteration and misbranding provisions in sections 501, 502, and 503 of the act. FDA is authorized to regulate approved new drugs and approved antibiotic drugs by regulations issued through informal rulemaking under sections 501, 502, and 503 of the act.

Subpart D -- Hearing Procedures for New Drugs

§ 314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.

(a) *Notice of opportunity for hearing.* The Director of the Center for Drugs and Biologics, Food and Drug Administration, will give the applicant, and all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, notice and an opportunity for a hearing on the Center's proposal to refuse to approve an application or to withdraw the approval of an application. The notice will state the reasons for the action and the proposed grounds for the order.

(1) The notice may be general (that is, simply summarizing in a general way the information resulting in the notice) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice).

(2) FDA will publish the notice in the Federal Register and will state that the applicant, and other persons subject to the notice under § 310.6, who wishes to participate in a hearing, has 30 days after the date of publication of the notice to file a written notice of participation and request for hearing. The applicant, or other persons subject to the notice under § 310.6, who fails to file a written notice of participation and request for hearing within 30 days, waives the opportunity for a hearing.

(3) It is the responsibility of every manufacturer and distributor of a drug product to review every notice of opportunity for a hearing published in the Federal Register to determine whether it covers any drug product that person manufactures or distributes. Any person may request an opinion of the applicability of a notice to a specific product that may be identical, related, or similar to a product listed in a notice by writing to the Division of Drug Labeling Compliance (HFN-310), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. A person shall request an opinion within 30 days of the date of publication of the notice to be eligible for an opportunity for a hearing under the notice. If a person requests an opinion, that person's time for filing an appearance and request for a hearing and supporting studies and analyses begins on the date the person receives the opinion from FDA.

(b) FDA will provide the notice of opportunity for a hearing to applicants and to other persons subject to the notice under § 310.6, as follows:

(1) To any person who has submitted an application, by delivering the notice in person or by sending it by registered or certified mail to the last address shown in the application.

(2) To any person who has not submitted an application but who is subject to the notice under § 310.6, by publication of the notice in the Federal Register.

(c) (1) *Notice of participation and request for a hearing, and submission of studies and comments.* The applicant, or any other person subject to the notice under § 310.6, who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, Rockville, MD 20857, (i) within 30 days after the date of the publication of the notice (or of the date of receipt of an opinion requested under paragraph (a)(3) of this section) a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the notice, unless a different period of time is specified in the notice of opportunity for a hearing, the studies on which the person relies to justify a hearing as specified in paragraph (d) of this section. The applicant, or other person, may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application or other report.

(2) FDA will not consider data or analyses submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the notice of opportunity for hearing and the results of the studies were not available within 60 days after the date of publication of the notice. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for a hearing. The person shall submit under paragraph (c)(1)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(3) Any other interested person who is not subject to the notice of opportunity for a hearing may also submit comments on the proposal to withdraw approval of the application. The comments are required to be submitted within the time and under the conditions specified in this section.

(d) The person requesting a hearing is required to submit under paragraph (c)(1)(ii) of this section the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on the refusal to approve an application is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in the application and in the format and containing the summaries required under § 314.50.

(1) If the grounds for FDA's proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, including any unfavorable analyses, views, or judgments with respect to the studies. No other data, information, or studies may be submitted.

(2) The submission is required to include a factual analysis of all the studies submitted. If the grounds for FDA's proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in § 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(3) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. FDA can most efficiently consider submissions made in the following format.

I. Safety data.

A. Animal safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

B. Human safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

II. Effectiveness data.

A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.

B. Combinations of individual active components.

1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by § 314.126.

2. An analysis showing clearly how each requirement of § 300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of § 300.50 or § 314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under § 314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in § 314.200(c)(2)) all studies and information specified in § 314.200(d).

(Warning: A willfully false statement is a criminal offense, *18 U.S.C. 1001.)*

(e) *Contentions that a drug product is not subject to the new drug requirements.* A notice of opportunity for a hearing encompasses all issues relating to the legal status of each drug product subject to it, including identical, related, and similar drug products as defined in § 310.6. A notice of appearance and request for a hearing under paragraph (c)(1)(i) of this section is required to contain any contention that the product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act, or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act or under section 107(c) of the Drug Amendments of 1962, or for any other reason. Each contention is required to be supported by a submission under paragraph (c)(1)(ii) of this section and the Commissioner of Food and Drugs will make an administrative determination on each contention. The failure of any person subject to a notice of opportunity for a hearing, including any person who manufactures or distributes an identical, related, or similar drug product as defined in § 310.6, to submit a notice of participation and request for hearing or to raise all such contentions constitutes a waiver of any contentions not raised.

(1) A contention that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is required to be supported by submission of the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product, unless FDA has waived a requirement for effectiveness (under § 314.126) or safety, or both. The submission should be in the format and with the analyses required under paragraph (d) of this section. A person who fails to submit the required scientific evidence required under paragraph (d) waives the contention. General recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(2) A contention that a drug product is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act, or under section 107(c) of

the Drug Amendments of 1962, is required to be supported by evidence of past and present quantitative formulas, labeling, and evidence of marketing. A person who makes such a contention should submit the formulas, labeling, and evidence of marketing in the following format.

I. Formulation.

A. A copy of each pertinent document or record to establish the exact quantitative formulation of the drug (both active and inactive ingredients) on the date of initial marketing of the drug.

B. A statement whether such formulation has at any subsequent time been changed in any manner. If any such change has been made, the exact date, nature, and rational for each change in formulation, including any deletion or change in the concentration of any active ingredient and/or inactive ingredient, should be stated, together with a copy of each pertinent document or record to establish the date and nature of each such change, including, but not limited to, the formula which resulted from each such change. If no such change has been made, a copy of representative documents or records showing the formula at representative points in time should be submitted to support the statement.

II. Labeling.

A. A copy of each pertinent document or record to establish the identity of each item of written, printed, or graphic matter used as labeling on the date the drug was initially marketed.

B. A statement whether such labeling has at any subsequent time been discontinued or changed in any manner. If such discontinuance or change has been made, the exact date, nature, and rationale for each discontinuance or change and a copy of each pertinent document or record to establish each such discontinuance or change should be submitted, including, but not limited to, the labeling which resulted from each such discontinuance or change. If no such discontinuance or change has been made, a copy of representative documents or records showing labeling at representative points in time should be submitted to support the statement.

III. Marketing.

A. A copy of each pertinent document or record to establish the exact date the drug was initially marketed.

B. A statement whether such marketing has at any subsequent time been discontinued. If such marketing has been discontinued, the exact date of each such discontinuance should be submitted, together with a copy of each pertinent document or record to establish each such date.

IV. Verification.

A statement signed by the person responsible for such submission, that all appropriate records have been searched and to the best of that person's knowledge and belief it includes a true and accurate presentation of the facts.

(Warning: A willfully false statement is a criminal offense, *18 U.S.C. 1001.)*

(3) The Food and Drug Administration will not find a drug product, including any active ingredient, which is identical, related, or similar, as described in § 310.6, to a drug product, including any active ingredient for which an application is or at any time has been effective or deemed approved, or approved under section 505 of the act, to be exempt from part or all of the new drug provisions of the act.

(4) A contention that a drug product is not a new drug for any other reason is required to be supported by submission of the factual records, data, and information that are necessary and appropriate to support the contention.

(5) It is the responsibility of every person who manufactures or distributes a drug product in reliance upon a "grandfather" provision of the act to maintain files that contain the data and information necessary fully to document and support that status.

(f) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drugs and Biologics, Food and Drug Administration, will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (g) (2) or (3) of this section will be submitted to the Office of the Commissioner of Food and Drugs for review and decision. When the Center for Drugs and Biologics recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drugs and Biologics recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and

representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drugs and Biologics has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with § 12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(g) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(1) Where a specific notice of opportunity for hearing (as defined in paragraph (a)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(2) When following a general notice of opportunity for a hearing (as defined in paragraph (a)(1) of this section) the Director of the Center for Drugs and Biologics concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(3) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drugs and Biologics concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(4) If review of the data, information, and analyses submitted show that the grounds cited in the notice are not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and rescind the notice of opportunity for hearing.

(5) If the Commissioner grants a hearing, it will begin within 90 days after the expiration of the time for requesting the hearing unless the parties otherwise agree in the case of denial of approval, and as soon as practicable in the case of withdrawal of approval.

(6) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(7) If the manufacturer or distributor of an identical, related, or similar drug product requests and is granted a hearing, the hearing may consider whether the product is in fact identical, related, or similar to the drug product named in the notice of opportunity for a hearing.

(8) A request for a hearing, and any subsequent grant or denial of a hearing, applies only to the drug products named in such documents.

(h) FDA will issue a notice withdrawing approval and declaring all products unlawful for drug products subject to a notice of opportunity for a hearing, including any identical, related, or similar drug product under § 310.6, for which an opportunity for a hearing is waived or for which a hearing is denied. The Commissioner may defer or stay the action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

§ 314.201 Procedure for hearings.

Parts 10 through 16 apply to hearings relating to new drugs under section 505 (d) and (e) of the act.

§ 314.235 Judicial review.

(a) The Commissioner of Food and Drugs will certify the transcript and record. In any case in which the Commissioner enters an order without a hearing under § 314.200(g), the record certified by the Commissioner is required to include the requests for hearing together with the data and information submitted and the Commissioner's findings and conclusion.

(b) A manufacturer or distributor of an identical, related, or similar drug product under § 310.6 may seek judicial review of an order withdrawing approval of a new drug application, whether or not a hearing has been held, in a United States court of appeals under section 505(h) of the act.

Subpart E -- Administrative Procedures for Antibiotics

§ 314.300 Procedure for the issuance, amendment, or repeal of regulations.

(a) The procedures in Part 10 apply to the issuance, amendment, or repeal of regulations under section 507 of the act.

(b) (1) The Commissioner of Food and Drugs, on his or her own initiative or on the application or request of any interested person, may publish in the Federal Register a notice of proposed rulemaking and order to issue, amend, or repeal any regulation contemplated by section 507 of the act.

The notice and order may be general (that is, simply summarizing in a general way the information resulting in the notice and order) or specific (that is, either referring to specific requirements in the statute and regulations with which there is a lack of compliance, or providing a detailed description and analysis of the specific facts resulting in the notice and order).

(2) The Food and Drug Administration will give interested persons an opportunity to submit written comments and to request an informal conference on the proposal, unless the notice and opportunity for comment and informal conference have already been provided in connection with the announcement of the reports of the National Academy of Sciences/National Research Council, Drug Efficacy Study Group, to persons who will be adversely affected, or as provided in § § 10.40(e) and 12.20(c)(2). A person is required to request an informal conference within 30 days of the notice of proposed rulemaking unless otherwise specified in the notice. If an informal conference is requested and granted, those persons participating in the conference may submit comments, within 30 days of the conference, unless otherwise specified in the proposal.

(3) It is the responsibility of every manufacturer and distributor of an antibiotic drug product to review every proposal published in the Federal Register to determine whether it covers any drug product that person manufactures or distributes.

(4) After considering the written comments, the results of any conference, and the data available, the Commissioner will publish an order in the Federal Register acting on the proposal, with an opportunity for any person who will be adversely affected to file objections, to request a hearing, and to show reasonable grounds for the hearing. Any person who wishes to participate in a hearing, shall file with the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, (i) within 30 days after the date of the publication of the order a written notice of participation and request for a hearing and (ii) within 60 days after the date of publication of the order, unless a different period of time is specified in the order, the studies on which the person relies to justify a hearing as specified in paragraph (b)(6) of this section. The person may incorporate by reference the raw data underlying a study if the data were previously submitted to FDA as part of an application or other report.

(5) FDA will not consider data or analysis submitted after 60 days in determining whether a hearing is warranted unless they are derived from well-controlled studies begun before the date of the order and the results of the studies were not available within 60 days after the date of publication of the order. Nevertheless, FDA may consider other studies on the basis of a showing by the person requesting a hearing of inadvertent omission and hardship. The person requesting a hearing shall list in the request for hearing all studies in progress, the results of which the person intends later to submit in support of the request for hearing. The person shall submit under paragraph (b)(4)(ii) of this section a copy of the complete protocol, a list of the participating investigators, and a brief status report of the studies.

(6) The person requesting a hearing is required to submit as required under § 314.200(c)(1)(ii) the studies (including all protocols and underlying raw data) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on a proposal is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in an application and in the format and containing the summaries required under § 314.50.

(i) If the grounds for DFA proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of § 314.126 and, for combination drug products, § 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under § 314.126. Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, any unfavorable analyses, views, or judgements with respect to the studies. No other data, information, or studies may be submitted.

(ii) The submission is required to include a factual analyses of all the studies submitted. If the grounds for FDA proposed action concern the effectiveness of the drug, the analysis is required to specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation established under § 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in § 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. If a study concerns a drug entity or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified.

(iii) Each person requesting a hearing shall submit an analysis of the data upon which the person relies, except that the required information relating either to safety or to effectiveness may be omitted if the notice of opportunity for hearing does not raise any issue with respect to that aspect of the drug; information on compliance with § 300.50 may be omitted if the drug product is not a combination drug product. FDA can most efficiently consider submissions made in the following format.

I. Safety data.

A. Animal safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

B. Human safety data.

1. Individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

2. Combinations of the individual active components.

a. Controlled studies.

b. Partially controlled or uncontrolled studies.

c. Documented case reports.

d. Pertinent marketing experiences that may influence a determination about the safety of each individual active component.

II. Effectiveness data.

A. Individual active components: Controlled studies, with an analysis showing clearly how each study satisfies, on a point-by-point basis, each of the criteria required by § 314.126.

B. Combinations of individual active components.

1. Controlled studies with an analysis showing clearly how each study satisfies on a point-by-point basis, each of the criteria required by § 314.126.

2. An analysis showing clearly how each requirement of § 300.50 has been satisfied.

III. A summary of the data and views setting forth the medical rationale and purpose for the drug and its ingredients and the scientific basis for the conclusion that the drug and its ingredients have been proven safe and/or effective for the intended use. If there is an absence of controlled studies in the material submitted or the requirements of any element of § 300.50 or § 314.126 have not been fully met, that fact is required to be stated clearly and a waiver obtained under § 314.126 is required to be submitted.

IV. A statement signed by the person responsible for such submission that it includes in full (or incorporates by reference as permitted in § 314.200(c)(2)) all studies and information specified in § 314.200(d).

(Warning: A willfully false statement is a criminal offense, *18 U.S.C. 1001.)*

(7) *Separation of functions.* Separation of functions commences upon receipt of a request for hearing. The Director of the Center for Drugs and Biologics will prepare an analysis of the request and a proposed order ruling on the matter. The analysis and proposed order, the request for hearing, and any proposed order denying a hearing and response under paragraph (b)(8) (ii) or (iii) of this section will be submitted to the Office of the Commissioner for review and decision. When the Center for Drugs and Biologics recommends denial of a hearing on all issues on which a hearing is requested, no representative of the Center will participate or advise in the review and decision by the Commissioner. When the Center for Drugs and Biologics recommends that a hearing be granted on one or more issues on which a hearing is requested, separation of functions terminates as to those issues, and representatives of the Center may participate or advise in the review and decision by the Commissioner on those issues. The Commissioner may modify the text of the issues, but may not deny a hearing on those issues. Separation of functions continues with respect to issues on which the Center for Drugs and Biologics has recommended denial of a hearing. The Commissioner will neither evaluate nor rule on the Center's recommendation on such issues and such issues will not be included in the notice of hearing. Participants in the hearing may make a motion to the presiding officer for the inclusion of any such issue in the hearing. The ruling on such a motion is subject to review in accordance with § 12.35(b). Failure to so move constitutes a waiver of the right to a hearing on such an issue. Separation of functions on all issues resumes upon issuance of a notice of hearing. The Office of the General Counsel, Department of Health and Human Services, will observe the same separation of functions.

(8) *Summary judgment.* A person who requests a hearing may not rely upon allegations or denials but is required to set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing with respect to a particular drug product specified in the request for hearing.

(i) Where a specific notice of opportunity for hearing (as defined in paragraph (b)(1) of this section) is used, the Commissioner will enter summary judgment against a person who requests a hearing, making findings and conclusions, denying a hearing, if it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the refusal to approve the application or the withdrawal of approval of the application; for example, no adequate and well-controlled clinical investigations meeting each of the precise elements of § 314.126 and, for a combination drug product, § 300.50, showing effectiveness have been identified. Any order entering summary judgment is required to set forth the Commissioner's findings and conclusions in detail and is required to specify why each study submitted fails to meet the requirements of the statute and regulations or why the request for hearing does not raise a genuine and substantial issue of fact.

(ii) When following a general notice of opportunity for a hearing (as defined in paragraph (b)(1) of this section) the Director of the Center for Drugs and Biologics concludes that summary judgment against a person requesting a hearing should be considered, the Director will serve upon the person requesting a hearing by registered mail a proposed order

denying a hearing. This person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iii) When following a general or specific notice of opportunity for a hearing a person requesting a hearing submits data or information of a type required by the statute and regulations, and the Director of the Center for Drugs and Biologics concludes that summary judgment against the person should be considered, the Director will serve upon the person by registered mail a proposed order denying a hearing. The person has 60 days after receipt of the proposed order to respond with sufficient data, information, and analyses to demonstrate that there is a genuine and substantial issue of fact which justifies a hearing.

(iv) If review of the data, information, and analyses submitted show that the basis for the order is not valid, for example, that substantial evidence of effectiveness exists, the Commissioner will enter summary judgment for the person requesting the hearing, and revoke the order. If a hearing is not requested, the order will become effective as published.

(v) If the Commissioner grants a hearing, it will be conducted under Part 12.

(vi) The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest.

(9) The repeal of any regulation constitutes a revocation of all outstanding certificates based upon such regulation. However, the Commissioner may, in his or her discretion, defer or stay such action pending a ruling on any related request for a hearing or pending any related hearing or other administrative or judicial proceeding.

(c) Whenever any interested person submits an application or request under section 507 of the act and Part 314 and FDA sends the person an approvable letter under § 314.110 or a not approvable letter under § 314.120, the person may file a petition proposing the issuance, amendment, or repeal of the regulation under the provisions of section 507(f) of the act and Part 10. The Commissioner shall cause the regulations proposed in the petition to be published in the Federal Register within 60 days of the receipt of an acceptable petition and further proceedings shall be in accord with the provisions of sections 507(f) and 701 (f) and (g) of the act and Part 10.

(d) (1) FDA will no promulgate a regulation providing for the certification of any batch of any drug composed wholly or in part of any kind of penicillin, streptomycin, chlortetracycline, chloramphenicol, bacitracin, or any other antibiotic drug, or any derivative thereof, intended for human use and no existing regulation will be continued in effect unless it is established by substantial evidence that the drug will have such characteristics of identity, strength, quality, and purity necessary to adequately ensure safety and efficacy of use. "Substantial evidence" has been defined by Congress to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions prescribed, recommended, or suggested in the labeling or proposed labeling thereof." This definition is made applicable to a number of antibiotic drugs by section 507(h) of the act and it is the test of efficacy that FDA will apply in promulgating, amending, or repealing regulations for all antibiotics under section 507(a) of the act as well.

(2) The scientific essentials of an adequate and well-controlled clinical investigation are described in § 314.126.

Subpart F -- Miscellaneous Provisions

§ 314.410 Imports and exports of new drugs and antibiotics.

(a) *Imports.* (1) A new drug or an antibiotic may be imported into the United States if: (i) It is the subject of an approved application under this part or, in the case of an antibiotic not exempt from certification under Part 433, it is also certified or released; or (ii) it complies with the regulations pertaining to investigational new drugs under Part 312; and it complies with the general regulations pertaining to imports under Subpart E of Part 1.

(2) A drug substance intended for use in the manufacture, processing, or repacking of a new drug may be imported into the United States if it complies with the labeling exemption in § 201.122 pertaining to shipments of drug substances in domestic commerce.

(b) *Exports.* (1) A new drug or an antibiotic may be exported if it is the subject of an approved application under this part, and, in the case of an antibiotic, it is certified or released, or it complies with the regulations pertaining to investigational new drugs under Part 312.

(2) A new drug substance that is covered by an application approved under this part for use in the manufacture of an approved drug product may be exported by the applicant or any person listed as a supplier in the approved application, provided the drug substance intended for export meets the specifications of, and is shipped with a copy of the labeling required for, the approved drug product.

(3) An antibiotic drug product or drug substance that is subject to certification under section 507 of the act, but which has not been certified or released, may be exported under section 801(d) of the act if it meets the following conditions:

(i) It meets the specifications of the foreign purchaser;

(ii) It is not in conflict with the laws of the country to which it is intended for export;

(iii) It is labeled on the outside of the shipping package that it is intended for export; and

(iv) It is not sold or offered for sale in the United States.

§ 314.420 Drug master files.

(a) A drug master file is a submission of information to the Food and Drug Administration by a person (the drug master file holder) who intends it to be used for one of the following purposes: To permit the holder to incorporate the information by reference when the holder submits an investigational new drug application under Part 312 or submits an application or an abbreviated application or an amendment or supplement to them under this part, or to permit the holder to authorize other persons to rely on the information to support a submission to FDA without the holder having to disclose the information to the person. FDA ordinarily neither independently reviews drug master files nor approves or disapproves submissions to a drug master file. Instead, the agency customarily reviews the information only in the context of an application under Part 312 or this part. A drug master file may contain information of the kind required for any submission to the agency, including information about the following:

(1) Facilities and operating procedures used to manufacture a drug substance or drug product;

(2) Drug substances or components used in the manufacture of a drug product, or drug products;

(3) Packaging materials;

(4) Components used in drug products, including colors, flavors, and essences; or

(5) Preclinical or clinical data.

(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the holder authorizes the incorporation in writing. Each incorporation by reference is required to describe the incorporated material by name, reference number, volume, and page number of the drug master file.

(c) A drug master file is required to be submitted in three copies. The agency has prepared under § 10.90(b) a guideline that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the holder shall notify in writing, each person authorized to reference that information. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in three copies and to describe by name, reference number, volume, and page number the information affected in the drug master file.

(d) The drug master file is required to contain a complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate. If the holder restricts the authorization to particular drug products, the list is required to include the name of each drug product and the application number, if known, to which the authorization applies.

(e) The public availability of data and information in a drug master file, including the availability of data and information in the file to a person authorized to reference the file, is determined under Part 20 and § 314.430.

§ 314.430 Availability for public disclosure of data and information in an application.

(a) The Food and Drug Administration will determine the public availability of any part of an application under this section and Part 20. For purposes of this section, the application includes all data and information submitted with or

incorporated by reference in the application, including investigational new drug applications, drug master files under § 314.420, supplements submitted under § 314.70, reports under § 314.80, and other submissions. For purposes of this section, safety and effectiveness data include all studies and tests of a drug on animals and humans and all studies and tests of the drug for identity, stability, purity, potency, and bioavailability.

(b) FDA will not publicly disclose the existence of an application before an approvable letter is sent to the applicant under § 314.110, unless the existence of the application has been previously publicly disclosed or acknowledged. The Center for Drugs and Biologics will maintain and make available for public disclosure a list of applications for which the agency has sent an approvable letter to the applicant.

(c) If the existence of an unapproved application has not been publicly disclosed or acknowledged, no data or information in the application is available for public disclosure.

(d) If the existence of an application has been publicly disclosed or acknowledged before the agency sends an approval letter to the applicant, no data or information contained in the application is available for public disclosure before the agency sends an approval letter, but the Commissioner may, in his or her discretion, disclose a summary of selected portions of the safety and effectiveness data that are appropriate for public consideration of a specific pending issue, for example, for consideration of an issue at an open session of an FDA advisory committee.

(e) After FDA sends an approval letter to the applicant, the following data and information in the application are immediately available for public disclosure, unless the applicant shows that extraordinary circumstances exist. A list of approved applications is publicly available from the Government Printing Office, Washington, DC 20402. The list is updated monthly.

(1) [Reserved]

(2) If the application applies to a new drug, all safety and effectiveness data previously disclosed to the public as set forth in § 20.81 and a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application. The summaries do not constitute the full reports of investigations under section 505(b)(1) of the act *(21 U.S.C. 355*(b)(1)) on which the safety or effectiveness of the drug may be approved. The summaries consist of the following:

(i) For an application approved before July 1, 1975, internal agency records that describe safety and effectiveness data and information, for example, a summary of the basis for approval or internal reviews of the data and information, after deletion of the following:

(*a*) Names and any information that would identify patients or test subjects or investigators.

(*b*) Any inappropriate gratuitous comments unnecessary to an objective analysis of the data and information.

(ii) For an application approved on or after July 1, 1975, a Summary Basis of Approval (SBA) document that contains a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. The SBA is prepared in one of the following ways:

(*a*) Before approval of the application, the applicant may prepare a draft SBA which the Center for Drugs and Biologics will review and may revise. The draft may be submitted with the application or as an amendment.

(*b*) The Center for Drugs and Biologics may prepare the SBA.

(3) A protocol for a test or study, unless it is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(4) Adverse reaction reports, product experience reports, consumer complaints, and other similar data and information after deletion of the following:

(i) Names and any information that would identify the person using the product.

(ii) Names and any information that would identify any third party involved with the report, such as a physician or hospital or other institution.

(5) A list of all active ingredients and any inactive ingredients previously disclosed to the public as set forth in § 20.81.

(6) An assay method or other analytical method, unless it serves no regulatory or compliance purpose and is shown to fall within the exemption established for trade secrets and confidential commercial information in § 20.61.

(7) All correspondence and written summaries of oral discussions between FDA and the applicant relating to the application, under the provisions of Part 20.

(8) All records showing the testing of an action on a particular lot of a certifiable antibiotic by FDA.

(f) All safety and effectiveness data and information which have been submitted in an application and which have not previously been disclosed to the public are available to the public, upon request, at the time any one of the following events occurs unless extraordinary circumstances are shown:

(1) No work is being or will be undertaken to have the application approved.

(2) A final determination is made that the application is not approvable and all legal appeals have been exhausted.

(3) Approval of the application is withdrawn and all legal appeals have been exhausted.

(4) A final determination has been made that the drug is not a new drug.

(5) For applications submitted under section 505(b) of the act, the effective date of the approval of the first application submitted under section 505(j) of the act which refers to such drug, or the date on which the approval of an application under section 505(j) which refers to such drug could be made effective if such an application had been submitted.

(6) For applications submitted under sections 505(j), 506, and 507 of the act, when FDA sends an approval letter to the applicant.

(g) The following data and information in an application are not available for public disclosure unless they have been previously disclosed to the public as set forth in § 20.81 or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information under § 20.61:

(1) Manufacturing methods or processes, including quality control procedures.

(2) Production, sales distribution, and similar data and information, except that any compilation of that data and information aggregated and prepared in a way that does not reveal data or information which is not available for public disclosure under this provision is available for public disclosure.

(3) Quantitative or semiquantitative formulas.

(h) The compilations of information specified in § 20.117 are available for public disclosure.

§ 314.440 Addresses for applications.

(a) Applicants shall send applications and other correspondence relating to matters covered by this part, except for products listed in paragraph (b) of this section, to the Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, and directed to the appropriate office identified below:

(1) An application under § 314.50 submitted for filing should be directed to the Document and Records Section (HFN-106). Applicants may obtain folders for binding applications from that office. After FDA has filed the application, the agency will inform the applicant which one of the divisions in the Office of New Drug Evaluation is responsible for the application. Amendments, supplements, resubmissions, requests for waivers, and other correspondence about an application that has been filed should be directed to the appropriate division.

(2) An abbreviated application under § 314.55, and amendments, supplements, resubmissions, and other correspondence about an abbreviated application should be directed to the Division of Generic Drugs (HFN-230). Applicants may obtain folders for binding abbreviated applications from that office.

(3) A request for an opportunity for a hearing under § 314.110 or § 314.120 on the question of whether there are grounds for denying approval of an application, except an application under paragraph (b) of this section, should be directed to the Division of Regulatory Affairs (HFN-360).

(b) Applicants shall send applications and other correspondence relating to matters covered by this part for the drug products listed below to the Office of Biologics Research and Review (HFN-825), Center for Drugs and Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, except applicants shall send a request for an

opportunity for a hearing under § 314.110 or § 314.120 on the question of whether these are grounds for denying approval of an application to the Director, Office of Biologics Research and Review (HFN-800), at the same address.

(1) Ingredients packaged together with containers intended for the collection, processing, or storage of blood and blood components.

(2) Urokinase products.

(3) Plasma volume expanders and hydroxyethyl starch for leukapheresis.

§ 314.445 Guidelines.

(a) The Food and Drug Administration prepares guidelines under § 10.90(b) to help persons comply with requirements in this part.

(b) The Center for Drugs and Biologics will maintain and make publicly available a list of guidelines that apply to the Center's regulations. The list states how a person can obtain a copy of each guideline. A request for a copy of the list should be directed to the Office of Consumer and Professional Affairs (HFN-10), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

PART 330 -- OVER-THE-COUNTER (OTC) HUMAN DRUGS WHICH ARE GENERALLY RECOGNIZED AS SAFE AND NOT MISBRANDED

9. Part 330 is amended in § 330.10 by revising paragraph (c), to read as follows:

§ 330.10 Procedures for classifying OTC drugs as generally recognized as safe and effective and not misbranded, and for establishing monographs.

* * * * *

(c) Information and data submitted under this section shall include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

PART 430 -- ANTIBIOTIC DRUGS; GENERAL

10. Part 430 is amended:

a. By revising Subpart B to read as follows:

Subpart B -- Antibiotic Drugs Affected by the Drug Amendments of 1962

§ 430.10 Certification or release of antibiotic drugs affected by the drug amendments of 1962.

(a) Before the 1962 amendments to it, the Federal Food, Drug, and Cosmetic Act only permitted the Food and Drug Administration to provide for the certification of batches of antibiotic drugs containing penicillin, streptomycin, chlortetracycline, chloramphenicol, or bacitracin, or any derivative of them. FDA certified those drugs under regulations promulgated on the basis of scientific proof of the drugs' safety and effectiveness. Most drugs containing an antibiotic other than one of those listed were subject to the new drug provisions of the act, which required that an applicant show that the drug was safe and obtain FDA approval of a new drug application before marketing it. An affirmative showing of effectiveness was not then required to obtain approval. Some antibiotic drugs that were not subject to certification, however, were also not subject to the new drug provisions of the act under informal FDA opinions that the drug was "not a new drug" or "no longer a new drug." FDA revoked those opinions under § 310.100 of this chapter.

(b) The 1962 amendments amended section 507 of the act to require the certification, release without certification, or exemption from certification, of all antibiotic drugs on the basis of scientific proof of safety and effectiveness. The amendments provided that FDA implement them for antibiotic drugs that were marketed on April 30, 1963 and were not subject to the certification provisions on that date. FDA is implementing the amendments with respect to antibiotic drugs formerly subject to the new drug provisions of the act through its Drug Efficacy Study Implementation (DESI) program under which the agency is evaluating those antibiotic drugs for efficacy. Until FDA completes that evaluation it will permit continued marketing of those antibiotic drugs under paragraph (c) of this section. The agency is also implementing the 1962 amendments with respect to antibiotic drugs formerly not subject to either the certification or new

drug provisions of the act and the agency is evaluating those antibiotic drugs for both safety and efficacy. Until FDA completes that evaluation, it will permit continued marketing of those antibiotic drugs under paragraph (d) of this section.

(c) Unless exempted from certification, FDA will certify or release antibiotic drugs which on April 30, 1963 were the subject of an approved new drug application under section 505 of the act, under regulations providing for certification of the drugs. Although the initial regulation for each of these drugs established under section 507(h) of the act was not conditioned upon an affirmative finding of the effectiveness of the drug, FDA is proceeding under its DESI program to amend or repeal those regulations to provide for certification of those drugs only if they had been shown to be both safe and effective.

(d) Unless exempted from certification, FDA will release without certification an antibiotic drug that was marketed on April 30, 1963, but not subject to certification, and not subject to an approved new drug application on that date, unless FDA has made a determination that the drug has not been shown to be safe or lacks substantial evidence of effectiveness under the DESI program. FDA is proceeding under its DESI program to establish regulations under section 507 to provide for certification of those drugs only if they have been shown to be safe and effective.

§ 430.20 [Removed]

b. By removing § 430.20 *Procedure for the issuance, amendment, or repeal of regulations.*

PART 431 -- CERTIFICATION OF ANTIBIOTIC DRUGS

11. Part 431 is amended:

§ 431.1 [Amended]

a. In § 431.1 *Requests for certification, check tests and assays, and working standards; information and samples required* by removing and reserving paragraph (b).

§ 431.16 [Removed]

b. By removing § 431.16 *Changes in facilities or controls; changes in mailing or promotional pieces.*

c. By revising § 431.17, to read as follows:

§ 431.17 Request to provide for certification of an antibiotic drug.

A request under section 507 of the Federal Food, Drug, and Cosmetic Act to provide for certification of an antibiotic drug is required to comply with the procedures and meet the requirements applicable to the submission to the Food and Drug Administration and review by the agency of applications and abbreviated applications, and amendments and supplements to them, under Part 314 of this chapter.

§ 431.50 [Amended]

d. In § 431.50 *Forms for certification or exemption of antibiotic drugs* by removing the entries for Form 5 and Form 6.

§ 431.60 [Removed]

e. By removing § 431.60 *Records and reports concerning experience with antibiotic drugs for human use for which a certificate or release has been issued.*

§ 431.70 [Amended]

f. In § 431.70 *Confidentiality of data and information in an investigational new drug notice for an antibiotic drug,* paragraphs (b) and (c) are amended by changing the references "§ 431.71" to "§ 314.430 of this chapter".

§ 431.71 [Removed]

g. By removing § 431.71 *Confidentiality of data and information in an antibiotic drug file.*

PART 433 -- EXEMPTIONS FROM ANTIBIOTIC CERTIFICATION AND LABELING REQUIREMENTS

§ 433.25 [Removed]

12. Part 433 is amended by removing § 433.25 *Antibiotic drugs intended for export.*

PART 510 -- NEW ANIMAL DRUGS

§ 510.3 [Amended]

8. Part 510 is amended:

a. In § 510.3 *Definitions and interpretations* in paragraph (1) by removing the words "and § 310.9 of this chapter".

b. In § 510.95 by revising the first sentence, to read as follows:

§ 510.95 Designated journals.

The following journals are available to the Food and Drug Administration and thus permit waiving of the submission of reprints and summaries covering reports contained in these journals to the extent that such requirements are waived in the regulations in this part:

* * * * *

PART 511 -- NEW ANIMAL DRUGS FOR INVESTIGATIONAL USE

13. Part 511 is amended in § 511.1 by revising paragraph (b)(4)(ii), to read as follows:

§ 511.1 New animal drugs for investigational use exempt from section 512 (a) of the act.

* * * * *

(b) * * *

(4) * * *

(ii) All labeling and other pertinent information to be supplied to the investigators. When such pertinent information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 514 -- NEW ANIMAL DRUG APPLICATIONS

14. Part 514 is amended:

a. In § 514.1 by revising paragraph (b)(12)(iii), to read as follows:

§ 514.1 Applications.

* * * * *

(b) * * *

(12) * * *

(iii) Will respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

b. In § 514.8 by revising paragraph (l), to read as follows:

§ 514.8 Supplemental new animal drug applications.

* * * * *

(l) A supplemental application that contains nonclinical laboratory studies shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

c. In § 514.15 by revising paragraph (c), to read as follows:

§ 514.15 Untrue statements in applications.

* * * * *

(c) Any nonclinical laboratory study contained in the application was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter, and the application fails to include a brief statement of the reason for the noncompliance.

d. In § 514.110 by revising paragraph (b)(8), to read as follows:

§ 514.110 Reasons for refusing to file applications.

* * * * *

(b) * * *

(8) It fails to include, with respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reasons for the noncompliance.

* * * * *

e. In § 514.111 by revising paragraph (a)(11), to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(11) Any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

* * * * *

f. In § 514.115 by revising paragraph (b)(4), to read as follows:

§ 514.115 Withdrawal of approval of applications.

* * * * *

(b) * * *

(4) That any nonclinical laboratory study that is described in the application and that is essential to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling, was not conducted in compliance with the good laboratory practice regulations as set forth in Part 58 of this chapter and no reason for the noncompliance is provided or, if it is, the differences between the practices used in conducting the study and the good laboratory practice regulations do not support the validity of the study.

* * * * *

PART 570 -- FOOD ADDITIVES

15. Part 570 is amended in § 570.35 by revising paragraph (c)(1)(vi), to read as follows:

§ 570.35 Affirmation of generally recognized as safe (GRAS) status.

* * * * *

(c) * * *

(1) * * *

(vi) If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each nonclinical study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

PART 571 -- FOOD ADDITIVE PETITIONS

16. Part 571 is amended:

a. In § 571.1 by revising paragraph (k), to read as follows:

§ 571.1 Petitions.

* * * * *

(k) If nonclinical laboratory studies are involved, petitions filed with the Commissioner under section 409(b) of the act shall include, with respect to each study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

b. In § 571.6 by revising the last sentence of the section to read as follows:

§ 571.6 Amendment of petition.

* * * If nonclinical laboratory studies are involved, additional information and data submitted in support of filed petitions shall include, with respect to each such study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason or the noncompliance.

PART 601 -- LICENSING

17. Part 601 is amended in § 601.2 by revising the first sentence of paragraph (a), to read as follows:

§ 601.2 Applications for establishment and product licenses; procedures for filing.

(a) *General.* To obtain a license for any establishment or product, the manufacturer shall make application to the Director, Office of Biologics Research and Review, on forms prescribed for such purposes, and in the case of an application for a product license, shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency; with respect to each nonclinical laboratory study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance; statements regarding each clinical investigation involving human subjects contained in the application, that it either was conducted in compliance with the requirements for institutional review set forth in Part 56 of this chapter or was not subject to such requirements in accordance with § 56.104 or § 56.105, and was conducted in compliance with requirements for informed consent set forth in Part 50 of this chapter; a full description of manufacturing methods; data establishing stability of the product through the dating period; sample(s) representative of the product to be sold, bartered, or exchanged or offered, sent, carried or brought for sale, barter, or exchange; summa-

ries of results of tests performed on the lot(s) represented by the submitted sample(s); and specimens of the labels, enclosures, and containers proposed to be used for the product. * * *

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PART 812 -- INVESTIGATIONAL DEVICE EXEMPTIONS

18. Part 812 is amended in § 812.27 by revising paragraph (b)(3), to read as follows:

§ 812.27 Report of prior investigations.

* * * * *

(b) * * *

(3) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice regulations in Part 58, or if any such study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. Failure or inability to comply with this requirement does not justify failure to provide information on a relevant nonclinical test study.

PART 1003 -- NOTIFICATION OF DEFECTS OR FAILURE TO COMPLY

19. Part 1003 is amended in § 1003.31 by revising paragraph (b), to read as follows:

§ 1003.31 Granting the exemption.

* * * * *

(b) Such views and evidence shall be confined to matters relevant to whether the defect in the product or its failure to comply with an applicable Federal standard is such as to create a significant risk of injury, including genetic injury, to any person and shall be presented in writing unless the Secretary determines that an oral presentation is desirable. Where such evidence includes nonclinical laboratory studies, the data submitted shall include, with respect to each such study, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance. When such evidence includes clinical investigations involving human subjects, the data submitted shall include, with respect to each clinical investigation either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with § 56.104 or § 56.105, and a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

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PART 1010 -- PERFORMANCE STANDARDS FOR ELECTRONIC PRODUCTS: GENERAL

20. Part 1010 is amended:

a. In § 1010.4 by revising paragraph (b)(1)(ix), to read as follows:

§ 1010.4 Variances.

* * * * *

(b) * * *

(1) * * *

(ix) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the good laboratory practice regulations set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

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b. In § 1010.5 by revising paragraph (c)(13), to read as follows:

§ 1010.5 Exemptions for products intended for United States Government use.

* * * * *

(c) * * *

(13) With respect to each nonclinical laboratory study contained in the application, either a statement that the study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a brief statement of the reason for the noncompliance.

* * * * *

Effective date. These regulations are effective May 23, 1985, except § 314.80 is effective August 22, 1985.

(Secs. 409, 501, 502, 503, 505, 506, 507, 512-516, 520, 701, 706, 52 Stat. 1049-1053 as amended, 1055, 1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended, 72 Stat. 1785-1788 as amended, 74 Stat. 399-407 as amended, 82 Stat. 343-351, 90 Stat. 540-560 *(21 U.S.C. 348, 351, 352, 353, 355, 356, 357, 360b-360f, 371, 376);* sec. 215, 301, 351, 354-360F, 58 Stat. 609, 702 as amended, 82 Stat. 1173-1186 as amended *(42 U.S.C. 216, 241, 262, 263b-236n)*

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

Dated: December 7, 1984.

[FR Doc. 85-4071 Filed 2-21-85; 8:45 am]

BILLING CODE 4160-01-M